

Web appendix: Supplementary material

Appendix A Results for Cox regression for treatment initiators at 3, 6, 9 months comparing nicotine replacement therapy (NRT), bupropion and varenicline

Outcome	Smoking cessation medicine	Total person years	No of events/ No of people prescribed product	Hazard ratio (95% CI)	
				Basic model, age, sex, year	Fully adjusted model
Fatal and non fatal self harm 3 mths	NRT	19196	69/78407	1	1
	Bupropion	1622	4/6568	0.62 (0.22,1.70)	0.83 (0.30,2.31)
	Varenicline	7363	19/30352	0.70 (0.41,1.18)	0.88 (0.52,1.49)
Fatal and non fatal self harm 6 mths	NRT	37515	131/78407	1	1
	Bupropion	3196	9/6568	0.71 (0.36,1.40)	0.93 (0.47,1.85)
	Varenicline	14239	39/30352	0.73 (0.50,1.05)	0.87 (0.59,1.26)
Fatal and non fatal self harm 9 mths	NRT	54839	199/78407	1	1
	Bupropion	4720	13/6568	0.69 (0.39,1.21)	0.92 (0.52,1.62)
	Varenicline	20550	59/30352	0.73 (0.54,0.99)	0.90 (0.66,1.22)
Depression 3mths	NRT	10315	799/42475	1	1
	Bupropion	961	40/3910	0.56 (0.41,0.77)	0.63 (0.46,0.87)
	Varenicline	4435	255/18386	0.69 (0.60,0.80)	0.75 (0.65,0.87)
Depression 6 mths	NRT	19999	1531/42475	1	1
	Bupropion	1883	92/3910	0.67 (0.54,0.83)	0.75 (0.60,0.92)
	Varenicline	8508	533/18386	0.78 (0.70,0.86)	0.83 (0.75,0.92)
Depression 9mths	NRT	29023	2204/42475	1	1

	Bupropion	2770	136/3910	0.69 (0.58,0.82)	0.77 (0.65,0.92)
	Varenicline	12182	776/18386	0.79 (0.72,0.86)	0.84 (0.77,0.92)
All cause mortality 3mths	NRT	19947	292/81496	1	1
	Bupropion	1665	5/6740	0.31 (0.13,0.74)	0.39 (0.16,0.95)
	Varenicline	7575	33/31227	0.37 (0.26,0.54)	0.44 (0.30,0.63)
All cause mortality 6mths	NRT	38978	541/81496	1	1
	Bupropion	3282	14/6740	0.46 (0.27,0.79)	0.58 (0.34,0.99)
	Varenicline	14647	60/31227	0.37 (0.29,0.49)	0.43 (0.33,0.57)
All cause mortality 9mths	NRT	56974	792/81496	1	1
	Bupropion	4848	19/6740	0.43 (0.27,0.68)	0.53 (0.34,0.84)
	Varenicline	21138	99/31227	0.43 (0.35,0.53)	0.49 (0.40,0.61)

Appendix B Distribution of baseline characteristics by smoking cessation medicine before and after matching on the propensity score

	% before matching		% after matching		% before matching		% after matching	
	Varenicline	NRT	Varenicline	NRT	Bupropion	NRT	Bupropion	NRT
FULLY ADJUSTED MODEL								
Female sex	50.3	54.3	50.3	50.3	50.9	54.3	50.9	50.4
Age category (mean)	1.87	2.04	1.87	1.87	1.84	2.04	1.84	1.84
Alcohol misuse	4.9	7.1	4.9	4.3	4.4	7.1	4.4	3.9
Hypnotics use (previous)	19.3	23	19.3	19	19	23	19	16.5
Antipsychotic use (previous)	15.8	21.1	15.8	15.2	15.6	21.1	15.6	14.6
Antidepressant use (previous)	41.1	47.7	41.1	41.5	41.9	47.7	41.9	40.8
Previous self harm	8.8	10.4	8.8	8.1	8.1	10.4	8.1	6.9
Previous smoking cessation	38.9	39.7	38.9	39.2	47.9	39.7	47.9	47.4
Mean category of GP visits per year	1.38	1.63	1.38	1.39	1.27	1.63	1.27	1.27
Treatment in 2007	17.2	30.8	17.2	17.6	46.7	30.8	46.7	47
Treatment in 2008	19.9	18	19.9	19.6	18.2	18	18.2	17.9
Treatment in 2009	21.2	16.8	21.1	20.9	12.3	16.8	12.3	12.2
Treatment in 2010	23.7	14	23.7	23.7	6.8	14	6.8	7.2
Treatment in 2011	18.2	10.3	18.2	18.2	4	10.3	4	3.7
Index of multiple deprivation score (mean)	3.2	3.3	3.2	3.2	3.1	3.3	3.1	3.1
Previous anxiolytic	18.2	21.9	18.3	17.5	19.3	21.9	19.3	17
Previous lithium	0.2	0.8	0.2	0.2	0.3	0.8	0.3	0.3
Previous drug misuse	1.8	3	1.8	1.6	1.9	3	1.9	1.4
Previous psychiatric illness	41.1	47.7	41.1	41.5	42.8	48.4	42.8	41.9
Previous chronic disease	32.1	38.1	32.1	32	29.6	38.1	29.6	28.9

Appendix C Results for propensity score analyses at 3, 6, 9 months comparing nicotine replacement therapy (NRT), bupropion and varenicline

VARENICLINE VS NRT				Hazard ratio (95% CI)	
Outcome	Smoking cessation medicine	Total person years	No of events/ No of people prescribed product	Basic model	Fully adjusted model
Fatal and non fatal self harm 3 mths	NRT	17026	61/69594	1	1
	Varenicline	7241	19/29784	0.70 (0.42,1.19)	0.87 (0.51,1.48)
Fatal and non fatal self harm 6 mths	NRT	33251	115/69594	1	1
	Varenicline	14033	39/29784	0.77 (0.53,1.12)	0.88 (0.60,1.28)
Fatal and non fatal self harm 9 mths	NRT	48569	176/69594	1	1
	Varenicline	20301	59/29784	0.76 (0.57,1.03)	0.90 (0.66,1.22)
Depression 3mths	NRT	9152	716/37694	1	1
	Varenicline	4333	249/17910	0.70 (0.60,0.81)	0.78 (0.67,0.90)
Depression 6 mths	NRT	17739	1367/37694	1	1
	Varenicline	8333	522/17910	0.78 (0.71,0.87)	0.86 (0.77,0.95)
Depression 9mths	NRT	25738	1968/37694	1	1
	Varenicline	11970	759/17910	0.79 (0.72,0.86)	0.86 (0.79,0.94)
All cause mortality 3mths	NRT	17715	260/72427	1	1
	Varenicline	7447	33/30637	0.31 (0.22,0.45)	0.37 (0.26,0.53)
All cause mortality 6mths	NRT	34594	478/72427	1	1
	Varenicline	14432	60/30637	0.31 (0.24,0.41)	0.36 (0.27,0.47)

All cause mortality 9mths	NRT Varenicline	50528 20879	687/72427 99/30637	1 0.36 (0.29,0.44)	1 0.41 (0.33,0.51)
---------------------------	--------------------	----------------	-----------------------	-----------------------	-----------------------

BUPROPION VS NRT

Outcome	Smoking cessation medicine	Total person years	No of events/ No of people prescribed product	Basic model	Fully adjusted model
Fatal and non fatal self harm 3 mths	NRT	18806	69/76833	1	1
	Bupropion	1570	4/6360	0.66 (0.24,1.83)	0.87 (0.31,2.40)
Fatal and non fatal self harm 6 mths	NRT	36738	129/76833	1	1
	Bupropion	3094	9/6360	0.80 (0.41,1.58)	1.00 (0.50,1.98)
Fatal and non fatal self harm 9 mths	NRT	53686	196/76833	1	1
	Bupropion	4568	12/6360	0.70 (0.39,1.25)	0.94 (0.53,1.66)
Depression 3mths	NRT	10019	786/41275	1	1
	Bupropion	923	40/3755	0.58 (0.42,0.80)	0.66 (0.48,0.90)
Depression 6 mths	NRT	19414	1506/41275	1	1
	Bupropion	1807	90/3755	0.67 (0.54,0.82)	0.76 (0.61,0.94)
Depression 9mths	NRT	28158	2167/41275	1	1
	Bupropion	2658	133/3755	0.68 (0.57,0.81)	0.78 (0.65,0.93)
All cause mortality 3mths	NRT	19543	292/79868	1	1
	Bupropion	1612	5/6526	0.25 (0.10,0.61)	0.34 (0.14,0.82)
All cause mortality 6mths	NRT	38176	541/79868	1	1
	Bupropion	3177	14/6526	0.38 (0.22,0.65)	0.51 (0.30,0.86)

All cause mortality 9mths	NRT	55782	791/79868	1	1
	Bupropion	4692	19/6526	0.35 (0.22,0.56)	0.47 (0.30,0.74)

Appendix D Distribution of potential confounders by physicians' prior prescription. Values are given in numbers (percentages) of patients unless otherwise specified

Variable	Nicotine replacement (n=78,712)	Bupropion (n=6528)	Varenicline (n=29,819)	Total (n=115,059)
Female sex	41956 (53.3)	3478 (53.3)	15583 (52.3)	61017 (53.0)
Median age (years)	45	45	44	45
Alcohol misuse	5039 (6.4)	353 (5.4)	1918 (6.4)	7310 (6.4)
Hypnotics use (previous)	17430 (22.1)	1367 (20.9)	6305 (21.1)	25102 (21.8)
Antipsychotic use (previous)	15531 (19.7)	1202 (18.4)	5532 (18.6)	22265 (19.4)
Antidepressant use (previous)	36328 (46.2)	2909 (44.6)	13302 (44.6)	52539 (45.7)
Previous self harm	7805 (9.9)	619 (9.5)	2962 (9.9)	11386 (9.9)
Previous smoking cessation treatment	32381 (41.1)	2774 (42.5)	10494 (35.2)	45649 (39.7)
Median No of clinical visits in year before Rx	17	17	16	17
Exposed to treatment before Jan 2008	31630 (40.2)	3715 (56.9)	4734 (15.9)	40079 (34.8)
Index of multiple deprivation score				
Missing	525 (0.7)	48 (0.7)	256 (0.9)	829 (0.7)
Least deprived quintile	10760 (13.7)	947 (14.5)	4102 (13.8)	15809 (13.7)
Most deprived quintile	18290 (23.2)	1287 (19.7)	7212 (24.2)	26789 (23.3)
Previous anxiolytic	16583 (21.1)	1355 (20.8)	5966 (20.0)	23904 (20.8)
Previous lithium	477 (0.6)	40 (0.6)	138 (0.5)	655 (0.6)
Previous drug misuse	2102 (2.7)	163 (2.5)	733 (2.5)	2998 (2.6)
Previous psychiatric illness	36576 (46.5)	2995 (45.9)	13532 (45.4)	53103 (46.2)
Previous chronic disease	28631 (36.4)	2319 (35.5)	10525 (35.3)	41475 (36.0)

Appendix E Association of confounders with actual prescription, physicians' previous prescription and indicators for the physicians' previous 7 prescriptions, adjusted for year of first prescription. Varenicline or bupropion vs nicotine replacement therapy.

	Actual prescriptions		Physicians' prior prescription		Indicators for seven previous prescriptions	
	F statistic	p value	F statistic	p value	F statistic	p value
Variable						
Female sex	52.98	<0.0001	0.65	0.52	1.14	0.32
Age category	128.83	<0.0001	4.56	0.01	1.70	0.05
Alcohol misuse	133.46	<0.0001	4.27	0.01	2.05	0.01
Hypnotics use (previous)	81.53	<0.0001	4.73	0.01	1.19	0.28
Antipsychotic use (previous)	164.04	<0.0001	6.68	<0.0001	1.33	0.18
Antidepressant use (previous)	130.87	<0.0001	6.09	<0.0001	1.17	0.29
Previous self harm	44.94	<0.0001	0.52	0.60	1.06	0.39
Previous smoking cessation treatment	54.88	<0.0001	10.55	<0.0001	2.37	<0.0001
GP visits in year before treatment	445.20	<0.0001	9.39	<0.0001	1.94	0.02
Index of multiple deprivation	16.76	<0.0001	6.21	<0.0001	3.04	<0.0001
Previous anxiolytic	68.66	<0.0001	2.66	0.07	1.23	0.25
Previous lithium	91.28	<0.0001	1.75	0.17	0.90	0.56
Previous drug misuse	79.32	<0.0001	2.60	0.07	1.16	0.30
Previous psychiatric illness	157.78	<0.0001	1.64	0.19	0.84	0.63
Previous chronic disease	171.44	<0.0001	2.21	0.11	0.98	0.47

Appendix F Results from instrumental variable analyses at 3, 6, 9 months comparing nicotine replacement therapy (NRT), bupropion and varenicline. This table includes the endogenous p value or Hausman test (i.e. whether there are any significant differences between the conventional regression model and the instrumental variable regression), the reported F statistics (i.e. the test of the association of the instrument and the prescription, if the value is >40 then the instrument is not weak) and the p value for the Hansen's J test (i.e. the test for over-identifying restrictions when multiple instruments are used).

	N	Smoking cessation medicine	Risk difference per 1000 (95% CI)	p value	Hausman test	F statistic	Hansen's J test
Outcome							
Fatal and non fatal self harm 3 mths	90926	NRT	0				
		Bupropion	-3.9 (-7.0, -0.9)	0.01	0.03	50.88	0.45
		Varenicline	0.4 (-0.8, 1.5)	0.52	0.27	681.52	0.14
Fatal and non fatal self harm 6 mths	85592	NRT	0				
		Bupropion	-3.9 (-9.0, 1.2)	0.13	0.16	46.41	0.51
		Varenicline	0.1 (-1.6, 1.8)	0.90	0.64	679.55	0.04
Fatal and non fatal self harm 9 mths	79483	NRT	0				
		Bupropion	-8.2 (-14.9, -1.5)	0.02	0.03	45.11	0.26
		Varenicline	-0.6 (-2.8, 1.7)	0.61	0.99	676.89	0.08
Depression 3mths	51165	NRT	0				
		Bupropion	-6.6 (-28.0, 14.8)	0.55	0.91	46.6	0.82
		Varenicline	-5.9 (-12.6, 0.8)	0.09	0.76	573.44	0.64
Depression 6 mths	48307	NRT	0				
		Bupropion	-7.8 (-39.4, 23.8)	0.63	0.92	40.93	0.31
		Varenicline	-5.1 (-15.1, 4.8)	0.31	0.67	566.46	0.63
Depression 9mths	45079	NRT	0				
		Bupropion	0.7 (-38.5, 39.9)	0.97	0.42	40.02	0.32
		Varenicline	-8.9 (-21.6, 3.7)	0.17	0.78	554.98	0.34
All cause mortality 3mths	94433	NRT	0				

		Bupropion	-4.2 (-10.5, 2.1)	0.19	0.53	51.88	0.18
		Varenicline	-0.8 (-2.8, 1.1)	0.41	0.08	677.35	0.76
All cause mortality 6mths	89061	NRT	0				
		Bupropion	-10.7 (-20.0, -1.4)	0.02	0.14	46.84	0.04
		Varenicline	0.5 (-2.7, 3.7)	0.76	<0.0001	671.1	0.51
All cause mortality 9mths	82857	NRT	0				
		Bupropion	-8.7 (-21.2, 3.8)	0.17	0.56	45.45	0.17
		Varenicline	0.7 (-3.3, 4.7)	0.73	<0.0001	662.86	0.09